Engineered-surface MOF nanoparticles for biomedical applications

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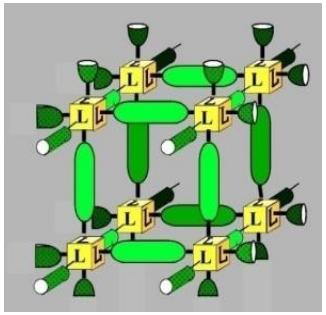
Outline

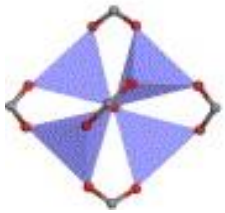
- ✓ MOFs introduction
- ✓ Presentation of MIL-100(Fe) NPs
- ✓ Heparin-engineered MIL-100(Fe) NPs
- ✓ Chitosan-engineered MIL-100(Fe) NPs

Coordination polymers or Metal Organic Frameworks (MOFs)

• **crystalline** coordination polymers built from **inorganic** units (transition metal, lanthanide, alkaline…) and **organic** linkers bearing several complexant groups (carboxylates, phosphonates, amines, bi/terpyridines, …) connected by exclusively **strong** interactions (ionocovalent)



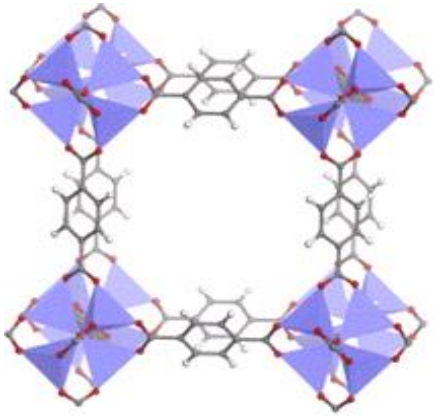
Inorganic part



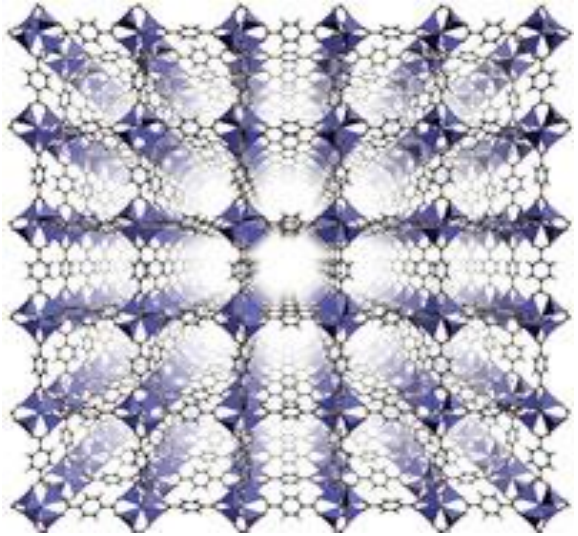
+

Organic linker (spacer)

« Self Assembly »



MOF-5



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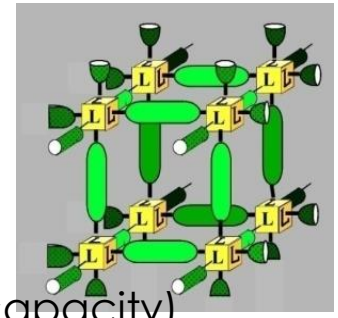
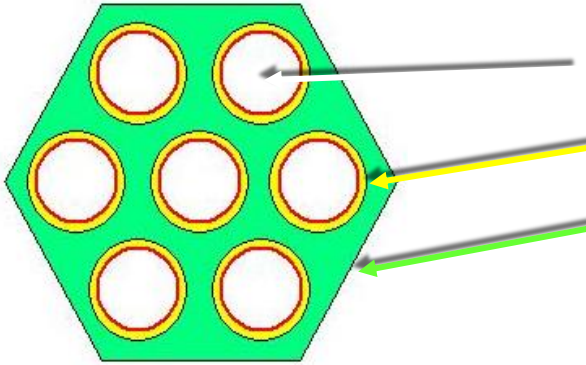
Coordination polymers or Metal Organic Frameworks (MOFs)



• **crystalline** coordination polymers built from **inorganic** units (transition metal, lanthanide, alkaline…) and **organic** linkers bearing several complexant groups (carboxylates, phosphonates, amines, bi/terpyridines, …) connected by exclusively **strong** interactions (ionocovalent)

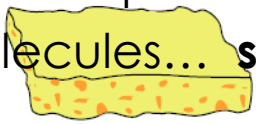
✓ these solids present cavities of various size and shape. (↑ storage capacity)

S_{area}= 500 - 6000 m^2/g, V_p = 0.5 - 3.5 cm^3/g, 3 - 60 Å



- narrow micro and mesoporosity… separation, storage
- ↑ internal surface… catalysis applications
- Highly versatile hybrid network

adapted to the adsorption of a large number of molecules… **sponge!**



✓ **Potential biomedical applications: imaging, biologically active gas release, drug/cosmetic delivery …**

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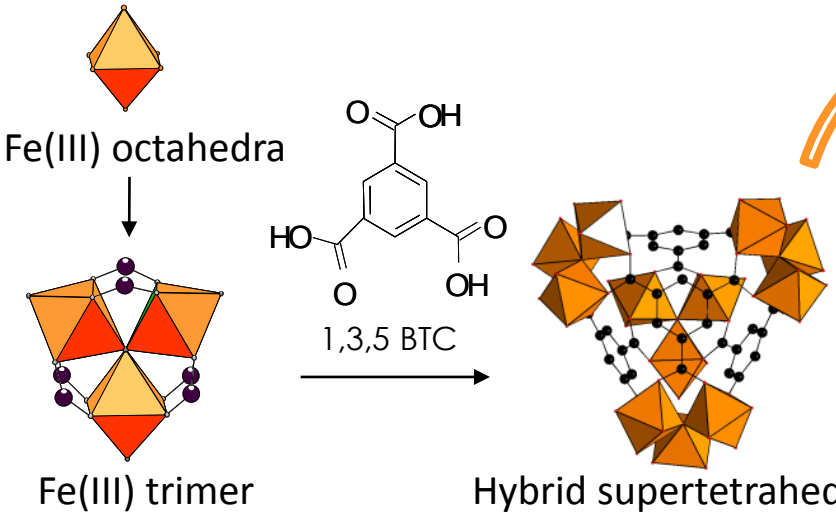
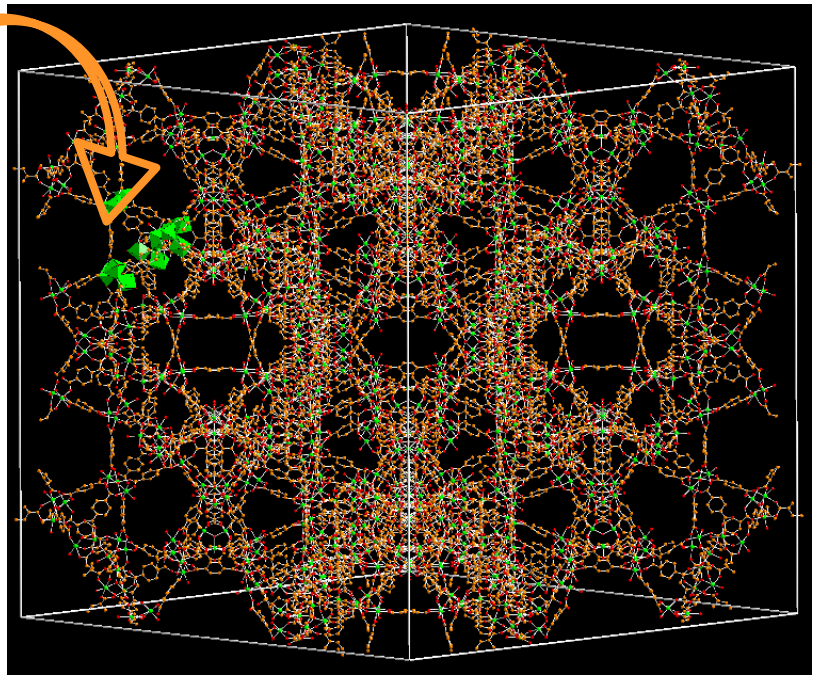
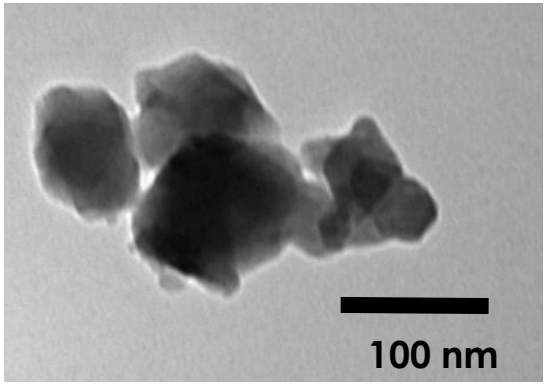
Horcajada et al, *Chem. Rev.*, 2012

Mesoporous iron(III) trimesate MIL-100 nanoparticles







Green-MW synthesis (6 min)
139 ± 25 nm PdI < 0.3
80% yield STY=12 ×·10^3 kg/m^3/d

Exceptional porosity: S_{BET}~1800 m^2/g; V_p~1.2 cm^3/g
Fe^{3+} Lewis acid CUS

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Horcajada et al, Chem. Commun. 2007; Garcia-Marquez et al, Eur J Inorg Chem, 2012

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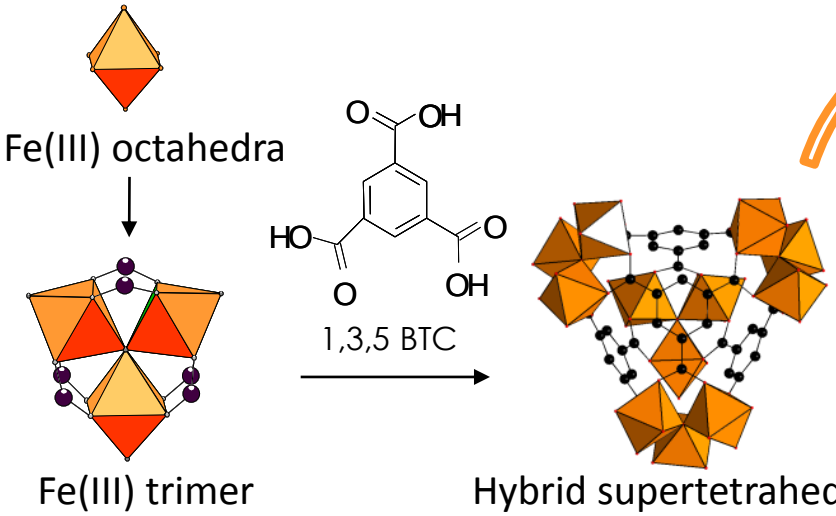
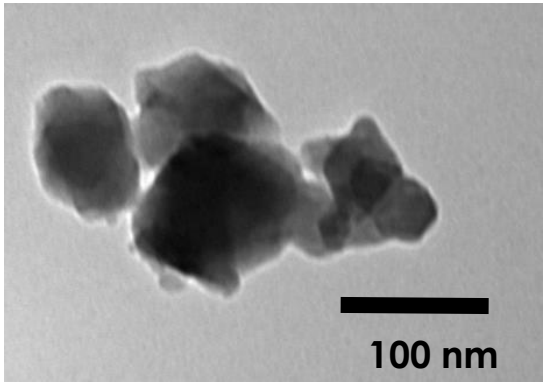
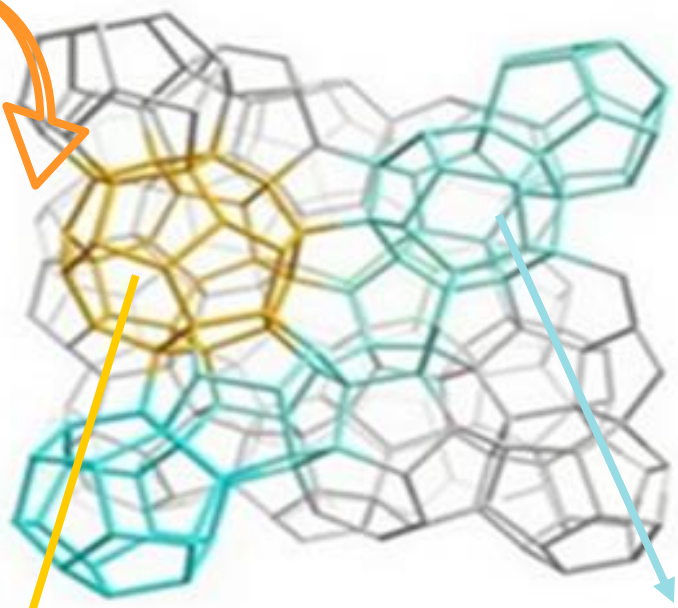
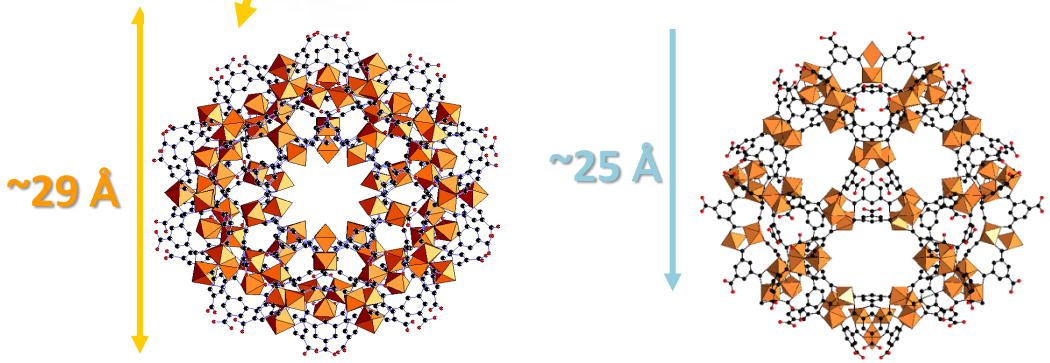
MIL-100 a=72.9 Å S.G. Fd-3m V=388 000 Å^3









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Horcajada et al, Chem. Commun. 2007; Garcia-Marquez et al, Eur J Inorg Chem, 2012

MIL-100 as promising drug nanocarrier

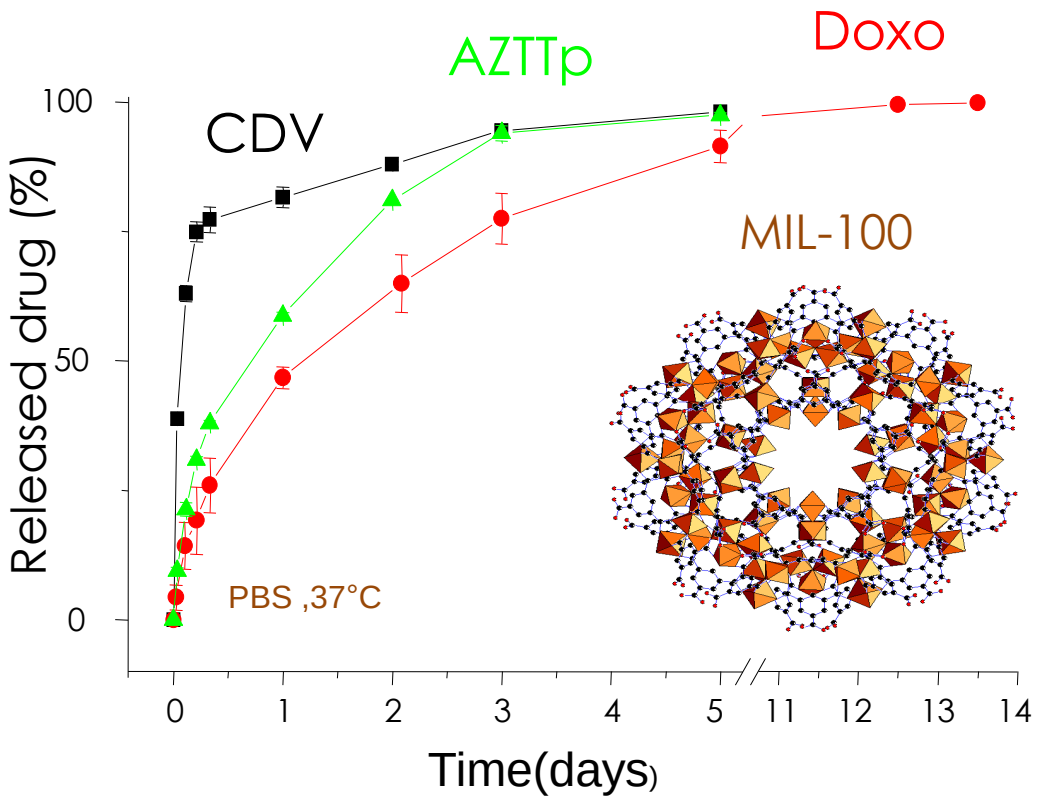
Coll. P Clayette, CEA
P. Couvreur, UP-Sud

Exceptional challenging drug payloads: 9-50 wt% of antitumor, antiretroviral, antibiotic

60x liposomes; 4-40x polymer

Progressive release in 5 to 14 days!

without « burst effect»



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Horcajada et al., *Nat. Mater.*, 2010; Agostoni et al, *Adv Healthc Mater*, 2013

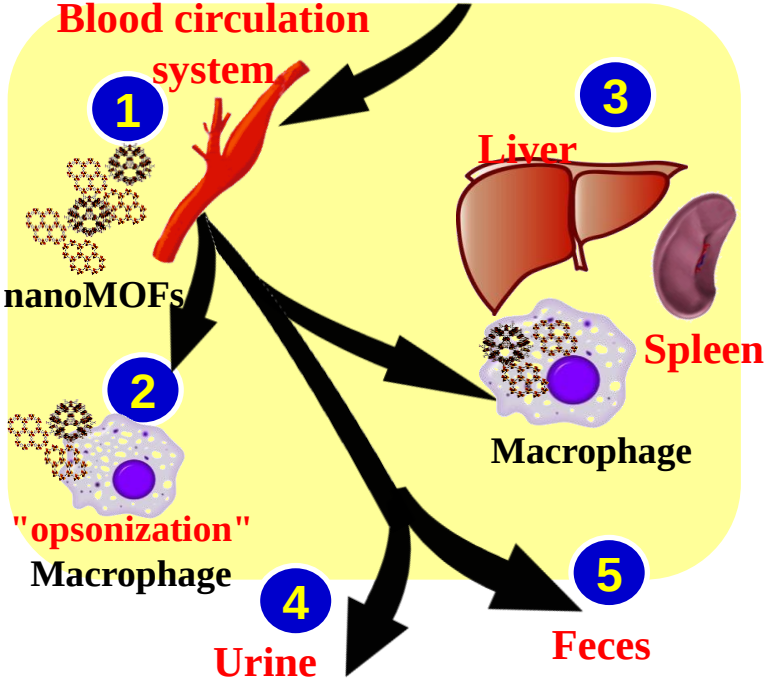
In vivo toxicity evaluation

Coll. P. Couvreur/R. Grei
(Chatenay Malabry)

Iv administration nanoMIL-100 (220 mg/kg)

1: After nanoMOFs iv administration
→hyperferritinemia
→compensation effect
→longer compensation leads to a ↓ [Fe] serum levels after 24h
→normal values after 7d

2: Adsorption of serum opsonins on the outer surface of nanoMOFs



3: Macrophages recognize opsonins-nanoMOFs
→phagocytosis, removing them from the blood circulation

→ ↑ [Fe,L] in RES (liver and spleen)

4-5 : MIL-100 degradation and excretion of Fe excess and trimesate ligand via urine and feaces → ↓ [Fe,L] in RES

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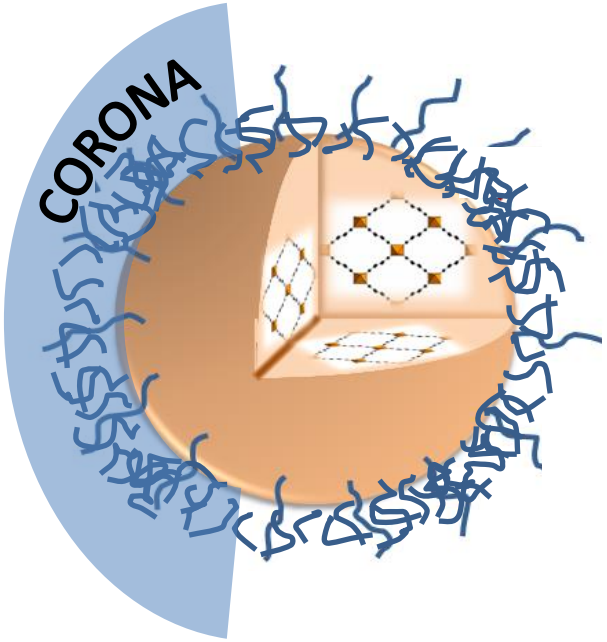
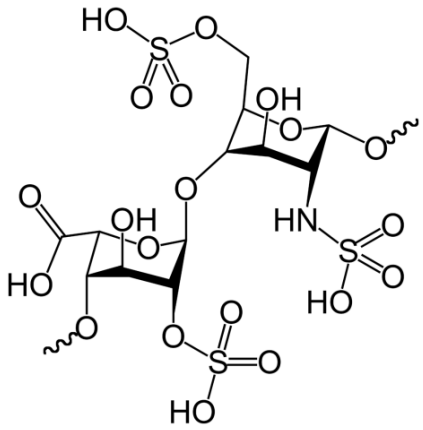
Horcajada et al, Nature Mater, 2010; Baati et al., Chem. Sci, 2013

Surface-engineering of MIL-100(Fe) nanoparticles



- ✓ Tuned biodistribution
- ✓ Higher colloidal stability
- ✓ Targeting abilities

HEPARIN



- **- charged polysacharide**
- **Anticoagulant**
- **NPs evasion from MPS**

Inhibit complement system

Hydrophilic →↓ Mϕ uptake

→ **Longer blood circulation times**

→ **Modify their *in vivo* fate**

Challenging specific outer surface functionalization in porous solids

1. **Localization in the MOF nanoparticle (superficial or intrusion inside the pores)**
   → reduce porosity and replace the encapsulated molecules
2. **Ability to promote a proper release of the drug encapsulated within the MOF**
3. **Stability of the coating**

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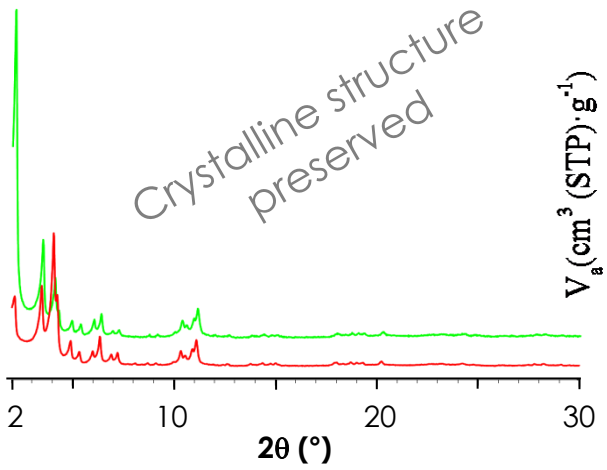
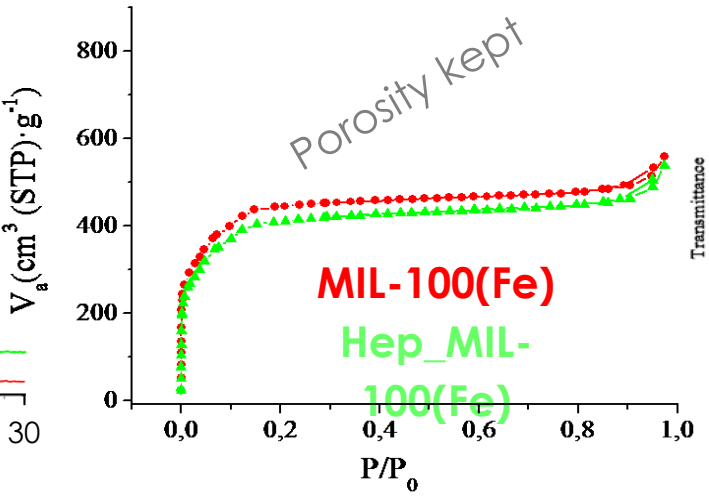
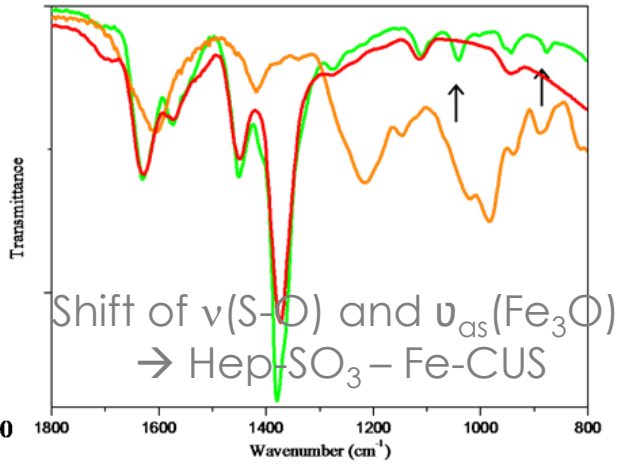
Patent FR12/55065, 2012.

Hep_MIL-100(Fe) physicochemical characterization

Simple and biocompatible impregnation method

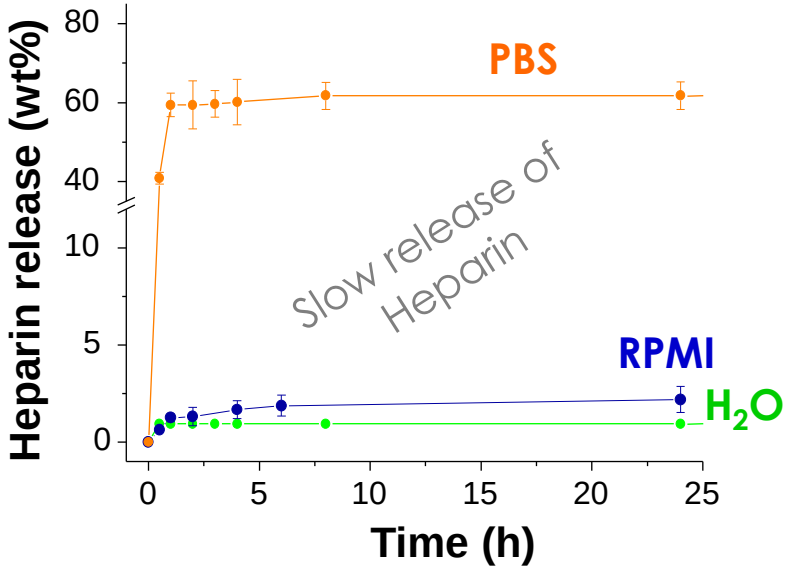






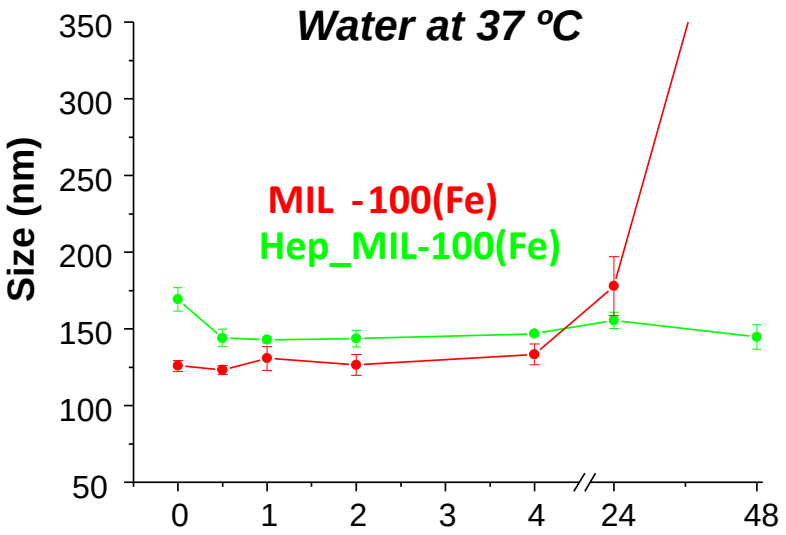
	MIL-100(Fe)	Hep_MIL-100(Fe)
Hep (wt%)		**12.5±1.5** (~ 88 eff)
Size (nm)	**141 ± 43**	**173 ± 51**
ξ-potential (mV)	**- 24.1 ± 2.1**	**– 20.7 ± 5.0**
S_{BET} (m^2/g)	**1530**	**1480**
Caffeine loading (wt%)	**43 ± 2**	**42 ± 6**

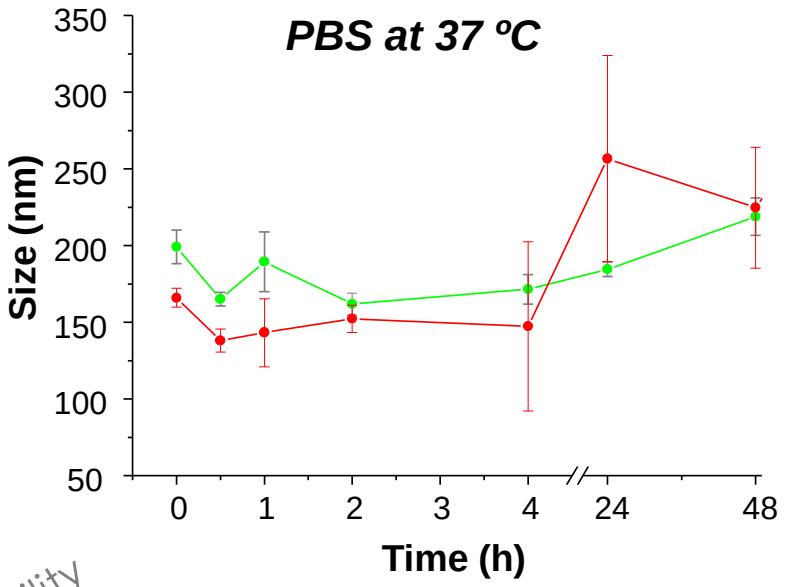
Heparin release

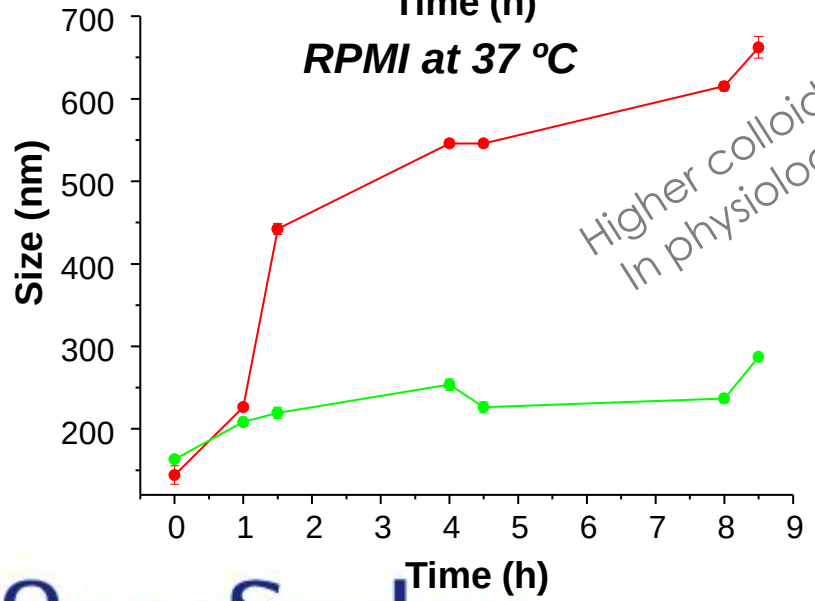


Density ~ 0.1 heparin chain / nm^2
Coating thickness ~ 15 nm
D between heparin chains ~ 3nm << R_F ~ 8.4 nm → « brush » conformation!

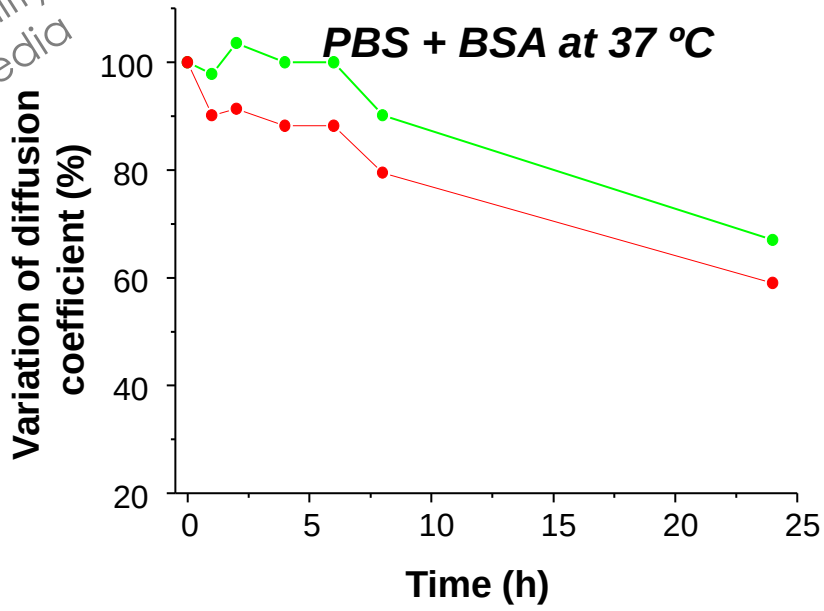
Hep_MIL-100(Fe) colloidal stability







Higher colloidal stability
In physiological media



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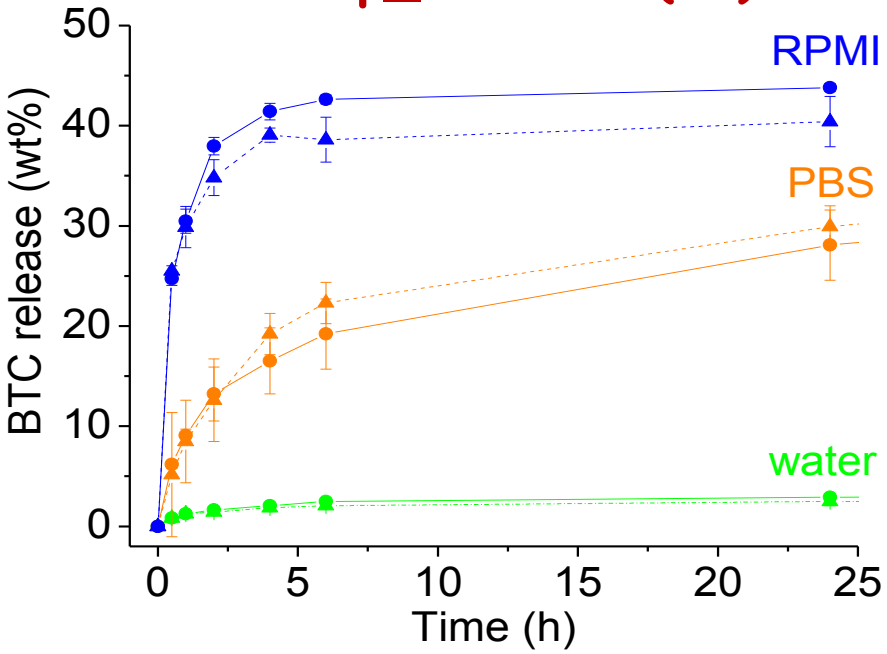
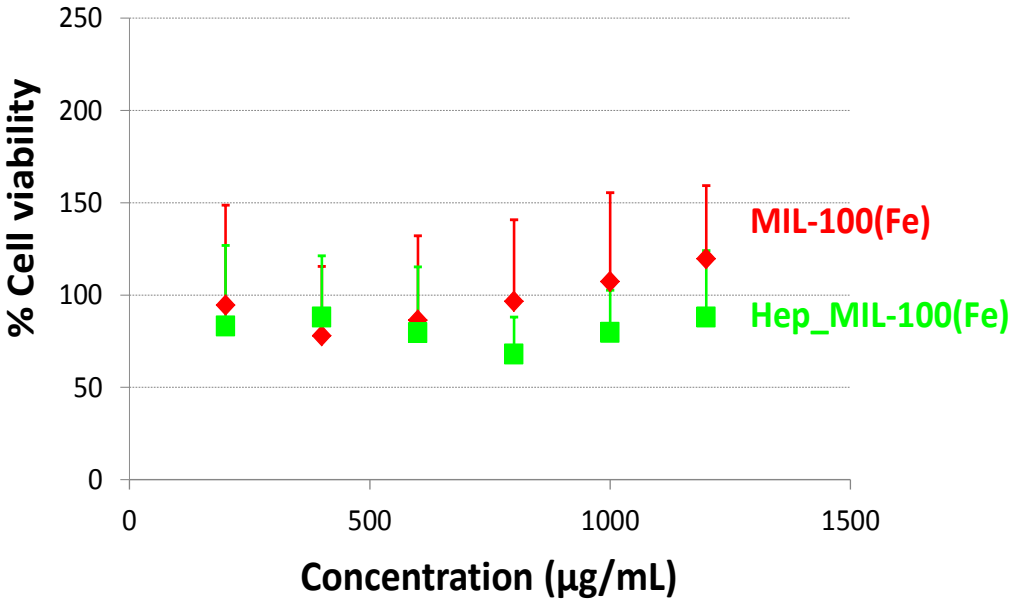
Hep_MIL-100(Fe): chemical stability, cell viability



MOF chemical stability
Independent on the heparin coating

MOF cytotoxicity
not affected



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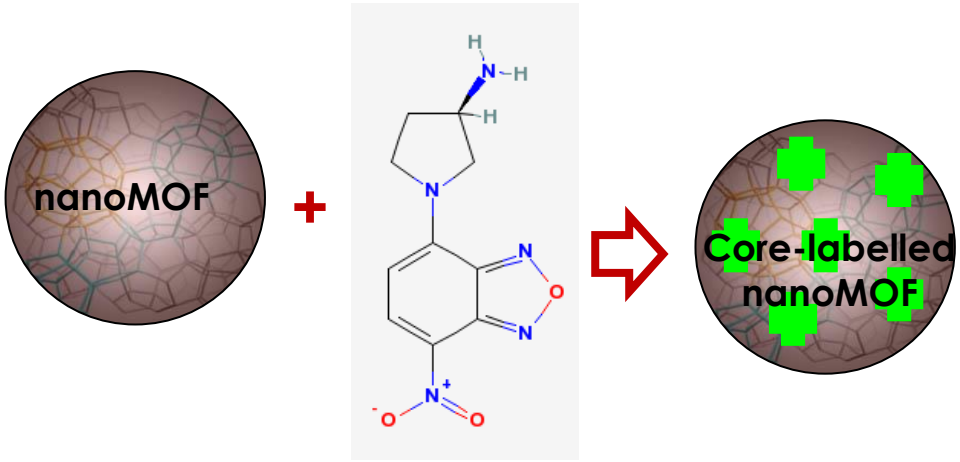
Hep_MIL-100(Fe): CK production (PBMs)

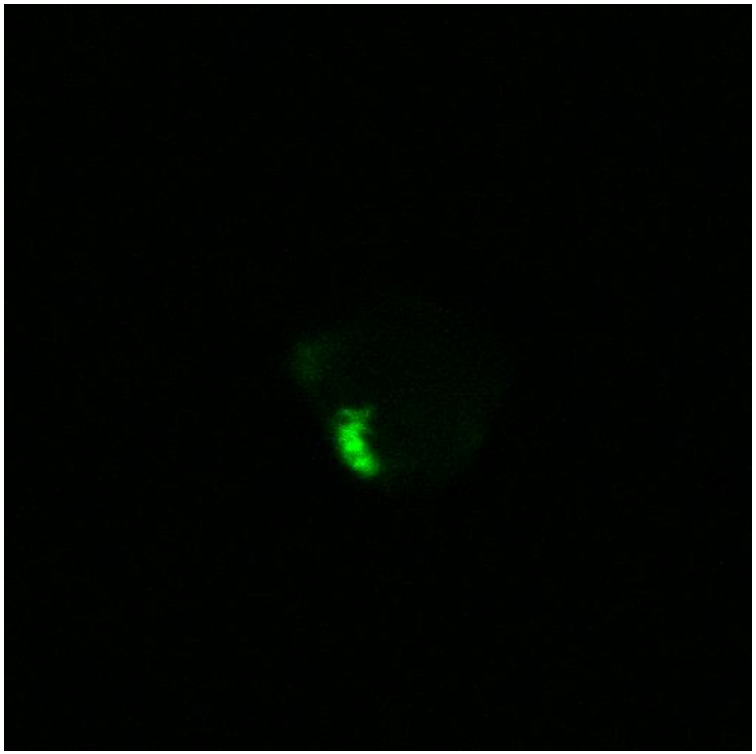
		NPs dose (µg/mL)	MIL-100(Fe)	Hep_MIL-100(Fe)
Type 1 cytokines	IL-12p70	25	1000	100
		250		10
	INF-γ	25	1000	0
		250		100
	IL-2	25	100	10
		250		0
	TNF-β	25	10	100
		250		
Type 2 cytokines	IL-10	25	1000	100000
		250		
	IL-6	25	100000	1000
		250		10000
Proinflammatory cytokines	IL-8	25	1000	1000
		250		10000
	IL-1β	25	10000	1000
		250		
	TNF-α	25	100000	100000
		250		

Lower cytokine production, (1/10 -1/100) with a dose dependent response

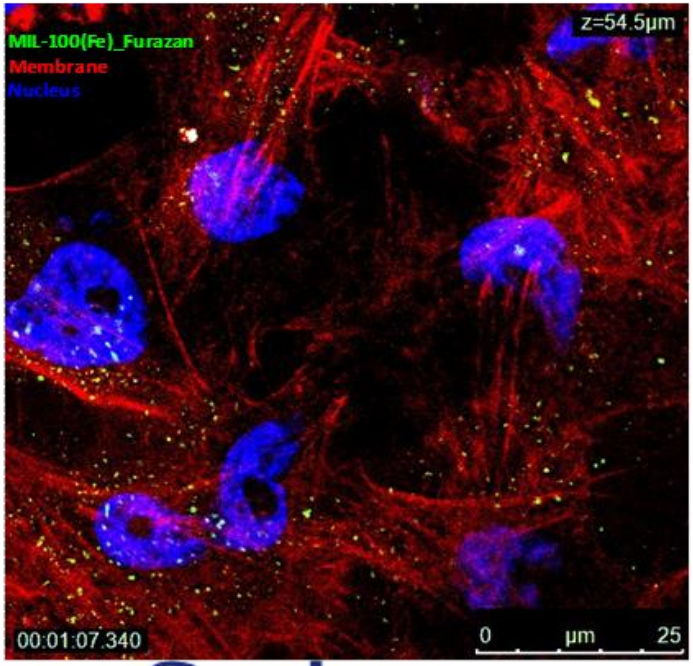
Hep_MIL-100(Fe) fluorescent labelling

Coll. M. Blanco, UNAV





2-13%wt of grafting



Fluorophore homogeneously distributed within the MOF particles

Small release (<20%) in cell culture medium after 24h

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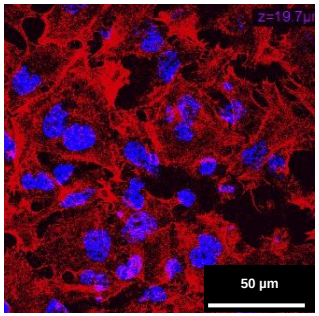
C.Tamames *et al.* *J Mater Chem B, 2013*

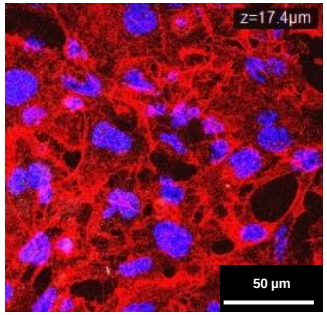
Hep_MIL-100(Fe) cell uptake

Free furazan 8h

Furazan

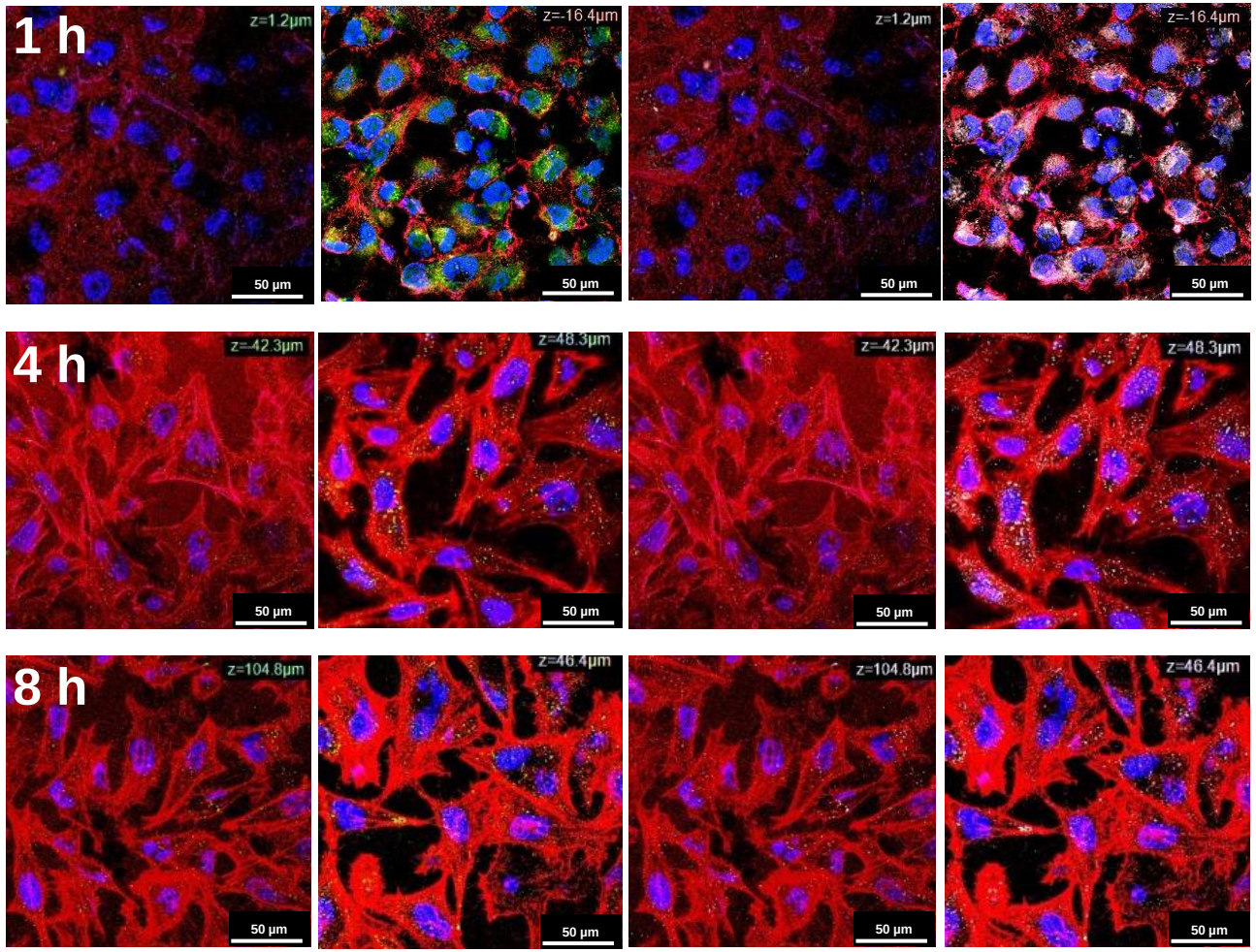


Fe self-reflection



Furazan | **Fe Self-reflection**

Hep_MIL-100(Fe) **MIL-100(Fe)** **Hep_MIL-100(Fe)** **MIL-100(Fe)**



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Cell uptake slowed-down by the heparin-coating in J774 macrophages

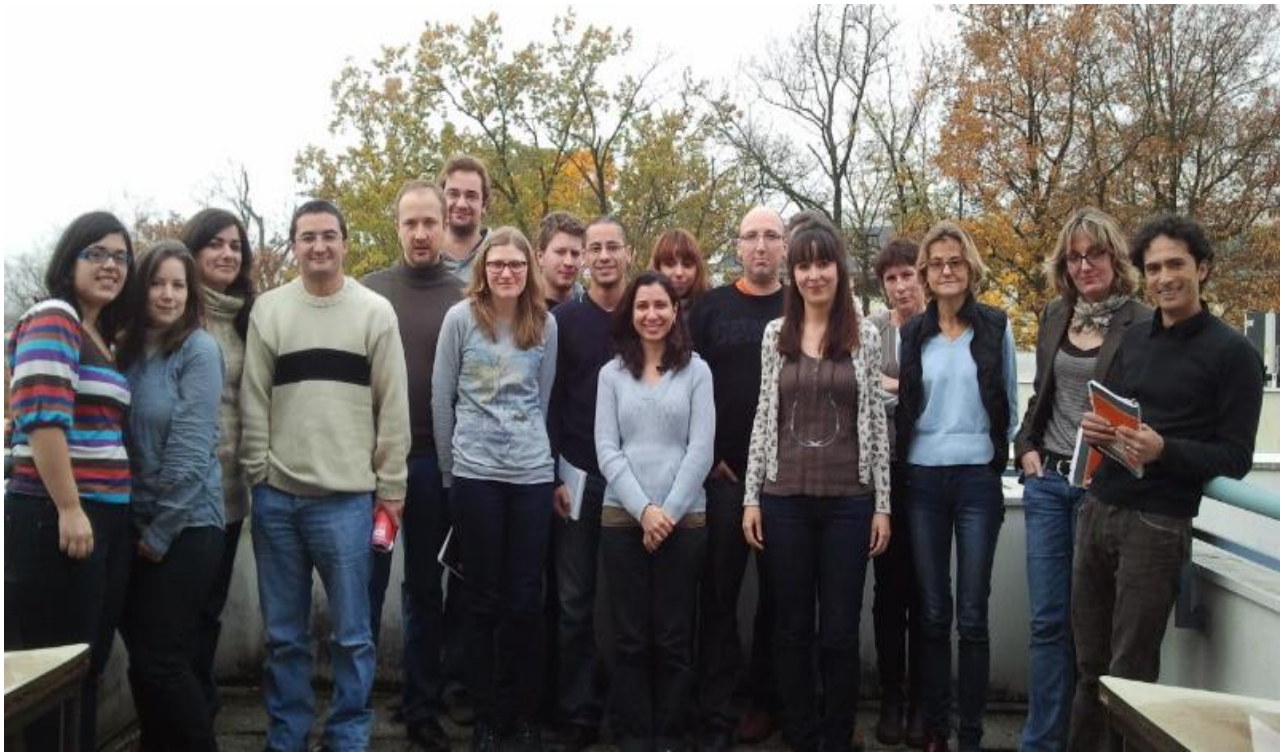
Conclusions

- ✓ *Efficient engineering-surface of MIL-100(Fe) NPs with heparin via a green one-pot method, allows preserving their structure and porosity, and so their drug nanocarrier performances*
- ✓ *Heparin coating endow MIL-100(Fe) NPs with improved biological properties → more stable colloidal solutions with both a lower immune response and slower macrophage uptake*
- ✓ *Biocompatible MIL-100 nanoparticles with exceptional drug loadings and controlled releases…*

→ *promising drug nanocarriers !*

Thanks to :

Institut Lavoisier C. Serre, E. Bellido, M. Gimenez-Marquez, A. Garcia-Marquez, D. Cunha, S. Mahammed-Daoud, T. Baati, T. Hidalgo, C. Tamames-Tabar, M Guillevic, MV Lozano



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